Autoimmunity Reviews 14 (2015) 769–773

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Recommendations on the use of biosimilars by the Brazilian Society of Rheumatology, Brazilian Society of Dermatology, Brazilian Federation of Gastroenterology and Brazilian Study Group on Inflammatory Bowel Disease—Focus on clinical evaluation of monoclonal antibodies and fusion proteins used in the treatment of autoimmune diseases

Valderílio Feijó Azevedo [a,*], Eduardo de Souza Meirelles [a], Jussara de Almeida Lima Kochen [a], Ana Cristina Medeiros [a], Sender J. Miszputen [c,d], Fábio Vieira Teixeira [d], Adérson Osmar Mourão Cintra Damião [d], Paulo Gustavo Kotze [d], Ricardo Romiti [b], Marcelo Arnone [b], Renata Ferreira Magalhães [b], Cláudia Pires Amaral Maia [b], André Vicente E. de Carvalho [b]

[a] Brazilian Society of Rheumatology, Brazil
[b] Brazilian Society of Dermatology, Brazil
[c] Brazilian Federation of Gastroenterology, Brazil
[d] Brazilian Study Group on Inflammatory Bowel Disease, Brazil

ARTICLE INFO

Article history:
Received 8 April 2015
Accepted 28 April 2015
Available online 1 May 2015

Keywords:
Biosimilars
Autoimmune diseases
Rheumatoid arthritis
Ankylosing spondylitis
Psoriasis
Crohn's disease

ABSTRACT

The Brazilian Societies of Rheumatology (SBR) and Dermatology (SBD), the Brazilian Federation of Gastroenterology (FBG) and the Brazilian Study Group on Inflammatory Bowel Disease (GEDIIB) gathered a group of their respective specialists on the topic of interest to discuss the most relevant issues regarding the clinical use of biosimilar medicines in Brazil. The main aim of that meeting was to prepare a document with recommendations to guide medical specialists and to help the national regulatory and policy-making agencies as concerns the authorization for marketing biosimilars used in autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, juvenile idiopathic arthritis and ulcerative colitis. In addition to considerations on the typical differences between innovator medicines and biosimilars, the specialists established a set of seven recommendations on regulatory advances related to clinical studies, indication extrapolation, nomenclature, interchangeability, automatic substitution and pharmacovigilance.

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* Corresponding author at: Rua Alvaro Alvim 224 casa 18, Seminário, Curitiba-Paraná CEP 80440-080, Brazil.
E-mail address: valderilio@hotmail.com (V.F. Azevedo).

http://dx.doi.org/10.1016/j.autrev.2015.04.014
1568-9972/

1. Introduction

Primarily aiming at producing a document with the main recommendations to guide medical specialists and to help regulatory and policy-making agencies as concerns the authorization for marketing biosimilars used in autoimmune diseases, the Brazilian Societies of Rheumatology ('Sociedade Brasileira de Reumatologia' — SBR) and Dermatology ('Sociedade Brasileira de Dermatologia' — SBD), the Brazilian Federation of Gastroenterology ('Federação Brasileira de Gastroenterologia' — FBG) and the Brazilian Study Group on Inflammatory Bowel Disease ('Grupo de Estudos da Doença Inflamatória Intestinal do Brasil' — GEDIIB) gathered their respective members who are experts in the subject of interest to discuss the most relevant topics regarding the clinical use of biosimilars in Brazil.

The group discussed the roles of physicochemical analysis and of pharmacodynamic, pharmacokinetic and toxicity studies, which are relevant steps to complete a full biosimilarity exercise and for totality-of-evidence analysis [1]. The group also stressed the wide consensus reached relative to such steps, which has already been incorporated by regulatory agencies in several countries, in addition to having been endorsed by the World Health Organization (WHO) in its guidelines [2]. However, the main issues the group discussed were the ones related with the development of clinical trials, nomenclature, interchangeability, automatic substitution, indication extrapolation and pharmacovigilance of biosimilars.

2. Biopharmaceuticals and biosimilars: From production to commercialization

Biopharmaceuticals, also known as immunobiologicals, are molecules obtained through biotechnological methods, such as DNA recombination or control of gene expression in living cells. The process of manufacturing biopharmaceuticals has crucial influence on the nature of the final product. Small differences in the design and execution of a manufacturing process have been long known to exert major influences on the clinical profile of the final product. Thus, most manufacturers of biopharmaceuticals obtain patents for the production process rather than for the product itself [3,4].

The main biopharmaceuticals used in the treatment of autoimmune diseases are monoclonal antibodies and fusion proteins. Specifically regarding the medical specialties involved in the present consensus, most of the used biopharmaceuticals were introduced in the pharmaceutical market between the end of the 90s and the beginning of the 21st century. The use of these agents is considered a watershed in the treatment of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis [5–7]. Biopharmaceuticals act by inhibiting relevant and specific therapeutic targets in the immune response, for which reason their use is gradually increasing worldwide [8]. Anti-tumor necrosis factor drugs (anti-TNFs) have proven to be quite safe and efficacious and thus have been included in the routine practices of specialists in rheumatology, dermatology and gastroenterology for the pharmacological treatment of patients. However, as the high cost of those drugs has significant impact on the health budgets of many countries [9], the demands for specific protocols for the use of biopharmaceuticals have been constant in both the public and private healthcare settings.

Following the recent expiration of the patents of some biopharmaceuticals that represented innovations from more than ten years ago, alternative versions of those products began to be produced. As such drugs are therapeutically equivalent in terms of clinical efficacy to the corresponding reference products and also exhibit similar safety profiles, they are called biosimilars. Manufacturers of biosimilars do not have access to the manufacturing process of the innovator biologics because they are the exclusive property of the innovating companies. Therefore, from a theoretical point of view, it is impossible for manufacturers of biosimilars to replicate a given protein exactly, unlike the production of generic drugs, whose small chemical molecules are identical to the original ones, and for which the analytical criteria are merely based on their chemical compositions [10,11].

For the past 10 years, we have witnessed significant advances in the regulations for the approval of biosimilars. All proposals from biosimilar development programs must support the biosimilarity between the proposed and reference products, including a rigorous assessment of the effects of any eventual differences between them, instead of attempting to independently establish the safety and efficacy of the proposed product [12]. The Brazilian RDC 55/2010 is the first piece of legislation in Latin America specific for biosimilars, and a large part of it follows the general guidelines formulated by the WHO [13]. Up to the time when the present consensus was prepared, no biosimilar monoclonal antibodies or fusion proteins had been approved in Brazil by this piece of legislation.

3. Biocomparability exercises

Due to the complexity of biopharmaceuticals and the limitations in the capacity of analytical techniques to establish whether they are actually identical to the reference product, the approval of biosimilars must necessarily depend on an unquestionable demonstration of comparable efficacy and clinical safety [4,14]. For the assessment of similarity, manufacturers must first perform a complete physicochemical and biological characterization of the biosimilars through a head-to-head comparison to the reference product. Ultimately, the physicochemical properties are assessed based on the compounds' structures [15]. According to European guidelines, any biological agent whose primary structure is not identical to the structure of the reference product cannot even be subjected to the biosimilar approval pathway [16]. In addition to the physicochemical characterization, the binding of the biosimilar to the cell receptor should be analyzed based on assays and animal studies, including pharmacodynamic and toxicity assessments. The methods used to establish the comparability of biosimilars to their reference products should be sufficiently selective and specific to be able to detect the differences between the two products. Ultimately, the actual relevance of such differences can only be fully established in preclinical and clinical studies [17].

4. Nomenclature

The name of a product is crucial for its unequivocal identification. The attribution of adverse effects and the maintenance of a suitable pharmacovigilance database are only possible when a product is distinguished from another by its name. The WHO systematized the nomenclature of pharmaceutical products by means of the International Nonproprietary Name (INN) [18]. According to this nomenclature, the INN of a biosimilar can be the same as the INN of its reference product. In such a case, however, if INN is used alone without further specific identifiers, the attribution of a given adverse effect to a definite product might become quite difficult, thus impairing the capacity of pharmacovigilance systems to accurately document the safety of biosimilars in the long term [19]. Within the Brazilian public health system, doctors must mandatorily prescribe biologics by their INN instead of their brand name, which is the current situation in several Latin American countries and